Clinical note

Unusual presentation of sarcoid-like reaction on bone marrow level associated with mediastinal lymphadenopathy on \(^{18}\)F-FDG-PET/CT resembling an early recurrence of Hodgkin's Lymphoma

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**Abstract**

\(^{18}\)F-FDG-PET/CT is widely employed to evaluate lymphoma patients. False positive results are quite frequent, generally due to active phase of inflammation. We describe an unusual PET/CT presentation of a sarcoid-like reaction (SLR) in a patient monitored for Hodgkin Lymphoma characterized by an intense uptake in lymph nodes and multiple bone foci in a PET/CT study. The final diagnosis was obtained by biopsy. This study draws attention to the fact that multifocal bone marrow uptakes due to a sarcoideal reaction may be a possible cause of false positive results in \(^{18}\)F-FDG-PET/CT studies in oncology patients.

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**Introduction**

In oncological patients, positron emission tomography/computed tomography with \(^{18}\)F-fluorodeoxyglucose (\(^{18}\)F-FDG-PET/CT) false positive results are frequently due to active granulomatous processes. \(^{18}\)F-FDG-PET/CT positive findings in sarcoid-like reaction (SLR) have already been documented in association with several malignancies, presenting either as pathological increased \(^{18}\)F-FDG uptake in lymph nodal, splenic, pulmonary, liver sites or with diffuse distribution pattern at bone marrow level. In the present case, \(^{18}\)F-FDG-PET/CT performed in a female young adult 3 months after the complete remission of Hodgkin's lymphoma (HL) recurrence, surprisingly documented lymph nodal and multifocal bone marrow pathological \(^{18}\)F-FDG uptakes. SLR was diagnosed by biopsy. To the best of our knowledge \(^{18}\)F-FDG-PET/CT positive findings in SLR was never documented as multifocal bone marrow uptake.

**Clinical case**

In 2007, HL nodular sclerosing type syncytial variant, stage III B, was diagnosed in a 27-year-old female. After 8 cycles of chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine, the patient showed a complete remission of disease.

In 2008, CT scan showed a supra-diaphragmatic lymph nodal relapse of HL, the patient was thus treated by 4 cycles of IGEV (ifosfamide, gemcitabine, vinorelbine and prednisone) followed by autologous stem cells transplantation.
Fig. 1. (a) FDG-PET/CT scan performed after chemotherapy (IGEV) and autologous stem cells transplantation for HL relapse, documented the absence of disease (coronal PET/CT fused images). (b) FDG-PET/CT scan after consolidation radiotherapy documented a supra- and sub-diaphragmatic lymph nodal involvement associated to multifocal bone marrow FDG uptake (coronal PET/CT fused images). (c) Sagittal view at spine level (PET and PET/CT fused image) showed uptake at spinous process of T12 (red arrows), chosen as a site for CT guided bone marrow biopsy. (d) Histological evidence of sarcoid like granuloma with central microfocus of fibrinoid necrosis (haemotoxulin and eosin, high power 40×). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).
One month after \(^{18}\text{F}-\text{FDG-PET/CT}\), a consolidation radiotherapy treatment at mediastinal level was performed for two months. A new \(^{18}\text{F}-\text{FDG-PET/CT}\) was performed three months after the end of radiotherapy to monitor the disease. Unexpectedly, \(^{18}\text{F}-\text{FDG-PET/CT}\) images documented a supra-diaphragmatic lymph nodal involvement with intense focal bone marrow \(^{18}\text{F}-\text{FDG}\) uptake in several skeletal districts (vertebrae, ribs, right sacrum, iliac bone and left pubis) (Fig. 1b). Since the patient presented allergy to CT iodinate contrast media, she was thus referred to MR imaging that confirmed \(^{18}\text{F}-\text{FDG-PET/CT}\) findings. The patient was then referred to bilateral bone marrow biopsy that showed the presence of a granulomatous reaction. In addition, based on \(^{18}\text{F}-\text{FDG-PET/CT}\) findings, a CT guided biopsy at bone level (left iliac bone and one dorsal vertebra) was performed (Fig. 1c), confirming the presence of chronic inflammatory process with evidence of sarcoid-like granulomatosis (Fig. 1d). Although the absence of clinical symptoms, diagnosis of SLR could be reached.

Mediastinal lymph node biopsy was not performed to avoid possible complications related to previous irradiation. A strict follow-up was thus scheduled.

During follow-up, a new MR imaging was comparable to the one performed two months before, both at lymph nodal and at bone levels. Three months later a new MRI imaging documented lymph nodal shrinking and the disappearance of bone marrow alterations. Approximately one year after the first \(^{18}\text{F}-\text{FDG-PET/CT}\), a new \(^{18}\text{F}-\text{FDG-PET/CT}\) showed a complete resolution of pathological uptake previously documented, according to a spontaneous resolution of SLR (data not shown).

Discussion

The emerging role of \(^{18}\text{F}-\text{FDG-PET/CT}\) as a powerful diagnostic tool for staging, restaging and response assessment of lymphoma has been recently confirmed by adding to International Working Group (IWG) criteria in evaluation response assessment.\(^1\)

\(^{18}\text{F}-\text{FDG-PET/CT}\) presents a higher sensitivity than morphological imaging in evaluating lymphoma patients. However, particularly in follow-up studies, this modality may present false positive results, thus determining a low specificity in detecting relapse of disease in HL patients.\(^2\)

To improve reliability of \(^{18}\text{F}-\text{FDG-PET/CT}\), Imaging Subcommittee of the International Harmonization Project in Lymphoma (ISHIPL) provided standardization criteria to perform and evaluate scans.\(^3\)

\(^{18}\text{F}-\text{FDG-PET/CT}\) false positive results are mostly due to active inflammation, in particular granulomatous processes. Among these, SLR is characterized by the development of non-caseating granulomas in tissues and lymph nodes, often noticed associated to neoplastic disease both during and after the end of treatment.\(^4\)

The pathogenesis of SLR has not been completely elucidated. It has been hypothesized that degenerative and necrotic changes within the tumoral lesions and releasing of humoral and T cell-mediated factors ultimately cause the recruitment and activation of macrophages resulting in granulomas development.\(^5\) Being related to an anti-neoplastic immune phenomenon, it is associated to a better prognosis.\(^6\) Conversely to sarcoidosis, SLR lacks systemic symptoms and does not require any treatment. The evidence of \(^{18}\text{F}-\text{FDG-PET/CT}\) positive findings in SLR, presenting with either diffuse lymph nodal, splenic, pulmonary or liver has been documented. Also at bone level, sarcoidosis has been described with diffuse pattern at spine and femoral level associated to HL.\(^7\) To the best of our knowledge this is the first case documenting a multifocal bone marrow pathological uptake related to SLR. According to guidelines of the ISHIPL that states that "clearly increased (multi) focal bone (marrow) uptake should be interpreted as positive for lymphoma", these findings should have been referred to neoplastic involvement.\(^8\) However, on the basis of clinical history, early recurrent disease was highly unlikely, and biopsy confirmation was indicated to reach a definitive diagnosis. Although clearly increased multifocal bone marrow uptake on PET scan are mostly due to a HL relapse, when clinical data do not support the diagnosis, SLR could be hypothesized as a possible alternative cause. A preliminary study has shown that oral prednisolone treatment, reducing FDG uptake in inflammatory tissue could be useful to differentiate flogistic and malignant uptake. This pharmacological test could not be used in the case of proven or suspected lymphoma, where such therapy could decrease FDG uptake in both inflammatory and cancer tissue.\(^8\) Particularly, HL presents peculiar architecture of the neoplastic tissue, where scattered tumoral cells named Reed Stenberg and Hodgkin cells (H-Rsc) are surrounded by a population of non-neoplastic mononuclear "bystander" cells, probably responsible for the immortalization of H-Rsc via chemokine production. Bystander cells have shown a very high metabolic activity in vitro causing impressive FDG avidity on PET scan in vivo. Behaving as a target for steroid action, bystander cells could cause early and remarkable response of HL to steroid treatment.\(^9\) A significant decrease in FDG uptake could be also determined at HL lesion, making thus unsuitable steroids pre-treatment to improve \(^{18}\text{F}-\text{FDG-PET/CT}\) specificity. Therefore, in HL patients biopical confirmation is mandatory to avoid improper management.

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References